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Convenient Synthesis of Some New Bi-heterocycles Containing 3-Aminoquinazolin-4(3H)-one and 1,2,4-Triazole Moieties

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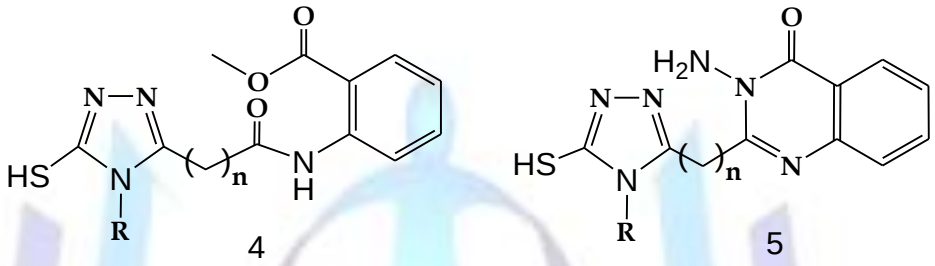
GRAPHICAL ABSTRACT:



Dicarboxylic acids, thiosemicarbazides and methylanthranilate were reacted to give methyl-2-(3-(5-mercapto-4-s-1,2,4-triazol-3-yl)-3-oxoalkylamino)benzoates **4**. The latters, have been cyclized with hydrazine hydrate to give 3-amino-2-((5-mercapto-4-substitued 1,2,4-triazol-3-yl)alkyl)quinazolin-4(3*H*)-ones **5** which expected to have biological effects.

Keywords: Thiocarbohydrazieds; methylanthranilate; methyl-2-(3-(5-mercapto-4-*S*-1,2,4-triazol-3-yl)-3-oxoalkylamino)benzoates and 3-amino-2-((5-mercapto-4-*S*-1,2,4-triazol-3-yl)alkyl)quinazolin-4(3*H*)-ones.

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INTRODUCTION:

Attention has been increasingly paid to the synthesis of bis-heterocyclic compounds, which exhibit various biological activities more than heterocyclic ones. These activities include antibacterial, fungicidal, tuberculostatic and plant growth regulative properties [1-6]. Also, it has been indicated in several reports that biquinazolinones have a wide range of applications in synthesis and as chiral building blocks [7, 8]. 4(3*H*)-Quinazolinones are known for more than a century [9]. Molecules based on quinazoline and quinazolinone exhibit multitude of interesting pharmacological activities [10], including anticonvulsant, antibacterial and antidiabetic activity [11, 12]. The important natural and synthetic 4(3*H*)-quinazolinones include *l*-vasicinone [13], chrysogine [14], methaquinolin [15], a sedative piriqualone [16-18], Febrifugine and *iso* febrifugine which possess this ring system were known as potent but toxic antimalarial agents long for than initial isolation [19] and recent chemical studies [20-23]. On the other hand, 1,2,4-triazole derivatives may exhibit different pharmacological activities such as anti-inflammatory, anti-fungal, anti-bacterial, and anti-viral. Some other 1,2,4-triazole derivatives have been reported to possess tuberculostatic, herbicidal and plant growth regulator activities [24-27]. In view of this the chemistry of bis-quinazolinones [28-31], and bis-4-amino-s-triazoles [32,33] was judicious to investigate the synthesis of asymmetric bis-heterocyclic compounds which have been unreported hitherto and are expected to possess biological activity [34-37].

RESULTS AND DISCUSSION:

Various new types of bis-heterocycles are having both 3-aminoquinazolinone and 1,2,4-triazole moieties were established through the synthesis of these research work via different routes. In the first route, the synthesis of 3-amino-2-((5-mercapto-4 substitued-1,2,4-triazol-3-yl)alkyl)quinazolin-4(3*H*)-ones **5a-j** took place via two steps: Firstly, the one pot reaction of thicarbohydrazide **1a,b**, the dicarboxlic acid **2**, and methylanthranilate **3** under fusion conditions afforded the corresponding methyl-2-(3-(5-mercapto-4-substitued-1,2,4-triazol-3-yl)-3-oxoalkylamino)benzoates **4a-j**. Secondly, refluxing of the mono amide intermediates **4a-j** with excess amount of hydrazine hydrate in n-butanol for 3-5 hours gave the target compound **5a-j** in a good yield. In the second route, the dicarboxylic acids **2** were refluxed with methyl anthranalate **3** in absolute ethanol to give methyl anthraniloyl mono carboxylates **6a-e** analogously, interaction of **6a-e** with thiocarbhydrazides **1a,b** under fusion conditions to give the corresponding mono amides **4a-j** which refluxed with hydrazine hydrate to afford **5a-j**. In the third route, the dicarboxylic acids **2** were refluxed with thiocarbhydrazides **1a,b** in absolute ethanol to give substituted-(4-methylthiosemicarbazido)-3-oxocarboxylic acids **7a-j** was interacted with methyl anthranalate **3** under fusion conditions to give the corresponding mono amides **4a-j**. The latters were refluxed with hydrazine hydrate to afford **5a-j** as mentioned above. Characterization of the newly synthesized compounds was elucidated owing to their spectral data IR, mass and ^{1}H NMR in addition to elemental analysis. (Scheme 1)

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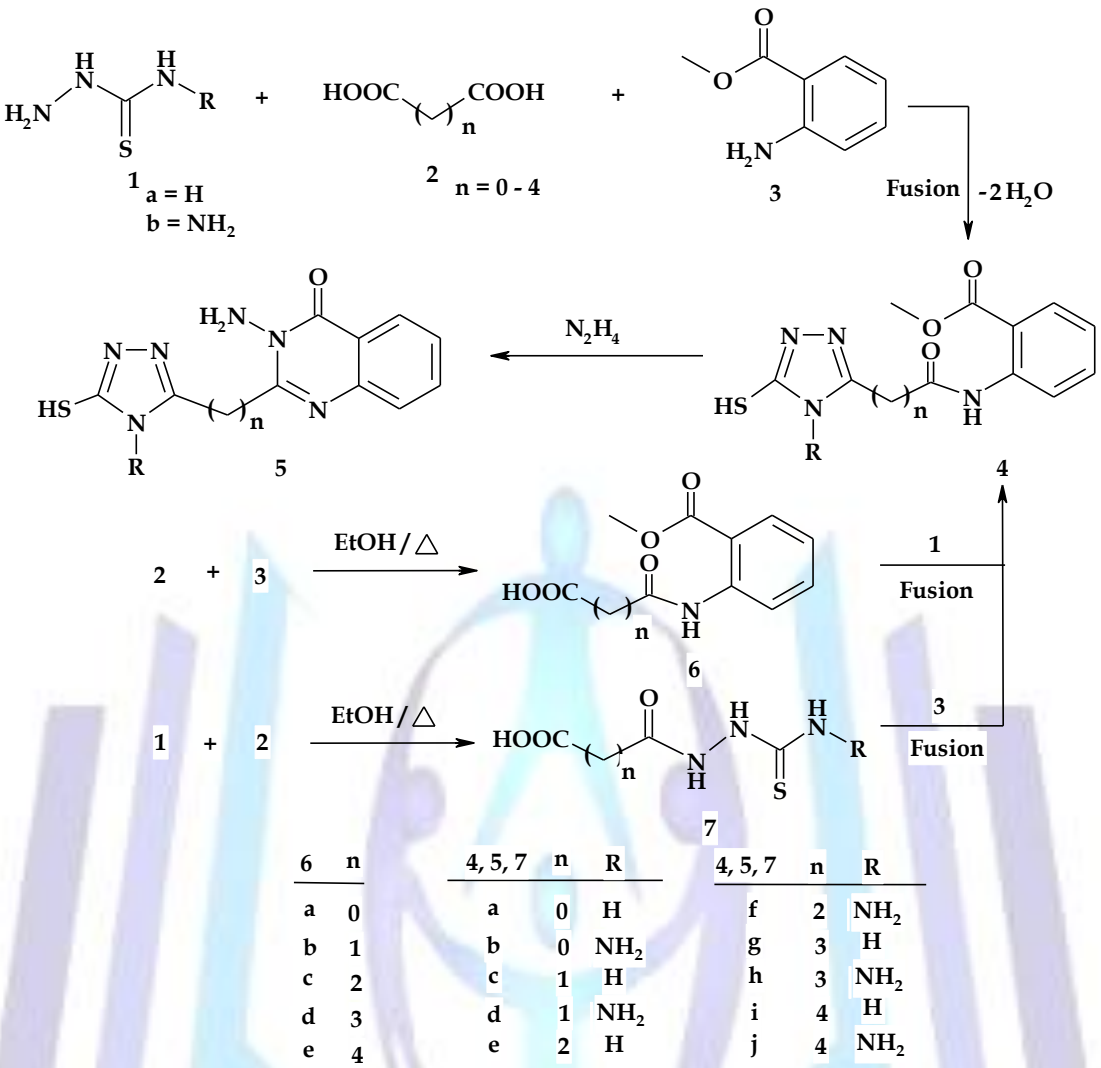


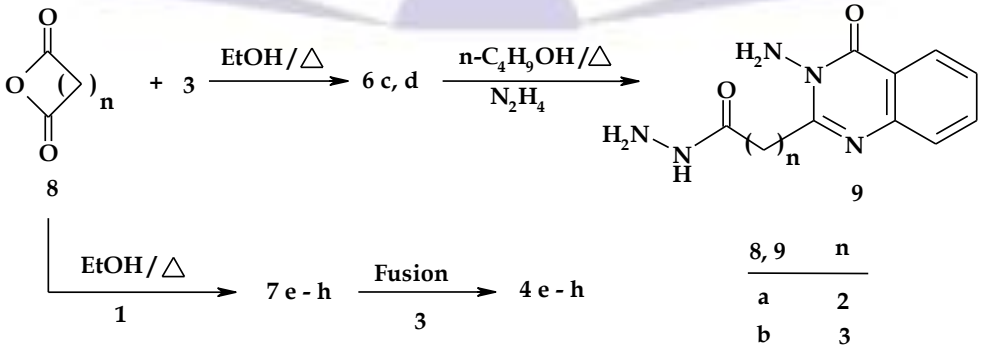
6	n
a	0
b	1
c	2
d	3
e	4

4, 5, 7	n	R
a	0	H
b	0	NH_2
c	1	H
d	1	NH_2
e	2	H

4, 5, 7	n	R
f	2	NH_2
g	3	H
h	3	NH_2
i	4	H
j	4	NH_2

Scheme 1

In the fourth route, substituted-(4-methylthiosemicarbazido)-3-oxocarboxylic acids **7e-h** could be obtained from boiling of dicarboxylic acid anhydrides **8a,b** with thiocarbhydrazides **1a,b**. The fusion of **7e-h** with methyl anthranalate **3** gave 2-(3-(5-mercapto-4-substitued-1,2,4-triazol-3-yl)-3-oxoalkylamino)benzoates **4e-h**. Finally, dicarboxylic acid anhydrides **8a,b** were refluxed with methyl anthranalate **3** to afford methyl anthraniloyl mono carboxylates **6c,d** which gave 3-(3,4-dihydro-3-amino-4-oxoquinazolin-2-yl)alkanehydrazides **9a,b** up on treatment with hydrazine hydrate. (Scheme 2)



8, 9	n
a	2
b	3

Scheme 2

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EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded (KBr disc) on a Shimadzu FT-IR 8201 PC Spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ or $(CD_3)_3SO$ on a Varian Gemini 200 MHz Spectrometer and chemical shifts were expressed in units using TMS as an internal reference. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Giza, Egypt, and National Research Centre.

Methyl-2-(3-(5-mercapto-4-s-1,2,4-triazol-3-yl)-3-oxoalkylamino) benzoates 4a-j:

Method (A): A mixture of semicarbazide or thiocarbohydrazide(0.005 mol) **1a,b**, dicarboxylic acids 2 (0.01 mol) and methylanthranilate **3** (0.005 mol) was heated in an oil bath at 170 ^{0}C for 30 min., the resulting solid was collected and recrystallized from ethanol to give the respective amides **4a-j**.

Method (B): The semicarbazide or thiocarbohydrazide(0.01 mol) and mono amides **6a-e** (0.01 mol),were heated in an oil bath at 170 ^{0}C for 30 min. the resulting solid was collected and recrystallized from ethanol to give the respective amides **4a-j**.

Method (C): The carboxylic acid derivatives **7a-j** (0.01 mol) and methylanthranilate (0.01 mol) were heated in an oil bath at 170 ^{0}C for 30 min. the resulting solid was collected and recrystallized from ethanol to give the respective amides **4a-j.**

3-Amino-2-[3-(4-amino-5-mercapto-4H-[1,2,4]traizol-3-yl)-alkyl]-3H-quinazolin-4-ones (5a-j):

The corresponding amides **4a-j** (0.01 mol) and 95% hydrazine hydrate (0.05 mol) were dissolved in n- butanol (30 ml) and refluxed for 6-8 hours. Cooling the reaction mixture in ice gave the crude product, which was filtered off and recrystallized to give compounds **5a-j.**

Methyl anthraniloyl mono carboxylates (6):

Method (A):

A mixture of the dicarboxylic acids **2** (0.01 mol) and methylanthranilate **3** (0.01 mol) was dissolved in ethanol and refluxed for 3-4 hours. After cooling, the precipitate so formed was filtered and recrystallized from the appropriate solvent to give **6a-e**.

Method (B):

A mixture of the acid anhydride **8a,b** (0.01 mol) and methylanthranilate 3 (0.01 mol) was dissolved in ethanol and refluxed for 3-4 hours. After cooling the precipitate so formed was filtered and recrystallized from the appropriate solvent to give **6c,d**.

Substituted-(4-methylthiosemicarbazido)-3-oxocarboxylic acids (7):

Method (A):

A mixture of the dicarboxylic acids **2** (0.01 mol) and semicarbazide or thiocarbohydrazide(0.01 mol),was dissolved in ethanol (30 ml) and refluxed for 4-5 hours. After cooling, the precipitate so formed was filtered and recrystallized from the appropriate solvent to give **7a-j.**

Method (B):

A mixture of the acid anhydride **8a,b** (0.01 mol) and semicarbazide or thiocarbohydrazide(0.01 mol),was dissolved in ethanol (30 ml) and refluxed for 4-5 hours. After cooling, the precipitate so formed was filtered and recrystallized from the appropriate solvent to give **7e-h**.

3-(3,4-dihydro-3-amino-4-oxoquinazolin-2-yl)alkanehydrazides (9a,b):

The corresponding amides **6a,b** (0.01 mol) and 95% hydrazine hydrate (0.05 mol) were dissolved in n- butanol (30 ml) and refluxed for 6-8 hours. Cooling in ice gave the crude product which was filtered off and recrystallized to give compounds **9a,b.**

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Table 1: Characterization Data of the Newly Synthesized Compounds

Compd. No.	Mp.◦C Solvent	Color Yield%	Mol. Formula (mol. Wt.)	Elemental analysis calcd. / found%			
				C	H	N	S
4a	235-36 EtOH	Colorless 77	$C_{11}H_{10}N_4O_3S$ (278.29)	47.48 47.50	3.62 3.60	20.13 20.11	11.52 11.50
4b	174-75 EtOH	Colorless 79	$C_{11}H_{11}N_5O_3S$ (293.30)	45.04 45.08	3.78 3.81	23.88 23.83	10.93 10.97
4c	223-25 EtOH	Colorless 80	$C_{12}H_{12}N_4O_3S$ (292.31)	49.31 49.36	4.14 4.16	19.17 19.20	10.97 10.94
4d	>300 EtOH	Colorless 82	$C_{12}H_{13}N_5O_3S$ (307.33)	46.90 46.93	4.26 4.30	22.79 22.75	10.43 10.49
4e	165-67 EtOH	Colorless 81	$C_{13}H_{14}N_4O_3S$ (306.34)	50.97 51.00	4.61 4.63	18.29 18.32	10.47 10.50
4f	233-35 EtOH	Colorless 83	$C_{13}H_{15}N_5O_3S$ (321.35)	48.59 48.56	4.70 4.73	21.79 21.81	9.98 10.01
4g	172-74 EtOH	Colorless 85	$C_{14}H_{16}N_4O_3S$ (320.37)	52.49 52.51	5.03 5.06	17.49 17.52	10.01 9.98
4h	227-29 EtOH	Colorless 86	$C_{14}H_{17}N_5O_3S$ (335.38)	50.14 50.16	5.11 5.13	20.88 20.90	9.56 9.58
4i	185-87 EtOH	Colorless 82	$C_{15}H_{18}N_4O_3S$ (334.39)	53.88 53.90	5.43 5.45	16.75 16.77	9.59 9.56
4j	244-45 EtOH	Colorless 74	$C_{15}H_{19}N_5O_3S$ (349.41)	51.56 51.59	5.48 5.50	20.04 20.06	9.18 9.15
5a	253-55 EtOH	Colorless 76	$C_{10}H_8N_6OS$ (260.28)	46.15 46.17	3.10 3.13	32.29 32.32	12.32 12.35
5b	282-84 EtOH	Colorless 69	$C_{10}H_9N_7OS$ (275.29)	43.63 43.66	3.30 3.32	35.62 35.59	11.65 11.62
5c	>300 EtOH	Colorless 73	$C_{11}H_{10}N_6OS$ (274.30)	48.17 48.20	3.67 3.70	30.64 30.61	11.69 11.71
5d	>300 EtOH	Colorless 76	$C_{11}H_{11}N_7OS$ (289.32)	45.67 45.62	3.83 3.88	33.89 33.91	11.08 11.10
5e	295-97 EtOH	Colorless 80	$C_{12}H_{12}N_6OS$ (288.33)	49.99 50.02	4.19 4.22	29.15 29.18	11.12 11.10
5f	244-46 EtOH	Colorless 66	$C_{12}H_{13}N_7OS$ (303.34)	47.51 47.53	4.32 4.30	32.32 32.35	10.57 10.53
5g	>300 EtOH	Colorless 75	$C_{13}H_{14}N_6OS$ (302.35)	51.64 51.66	4.67 4.65	27.80 27.83	10.61 10.63
5h	235-37 EtOH	Colorless 81	$C_{13}H_{15}N_7OS$ (317.37)	49.20 49.18	4.76 4.78	30.89 30.91	10.10 10.12

5i	>300	Colorless	$C_{14}H_{16}N_6OS$	53.15	5.10	26.56	10.13
	EtOH	78	(316.38)	53.13	5.14	26.53	10.11
5j	288-90	Colorless	$C_{14}H_{17}N_7OS$	50.74	5.17	29.59	9.68
	EtOH	73	(331.40)	50.77	5.19	29.61	9.71
6a	98-100	Colorless	$C_{10}H_9NO_5$ (223.18)	53.82	4.06	6.28	--
	EtOH	73		53.85	4.03	6.26	--
6b	96-98	Colorless	$C_{11}H_{11}NO_5$ (237.21)	55.70	4.67	5.90	--
	EtOH	78		55.73	4.64	5.92	--
6c	95-97	Colorless	$C_{12}H_{13}NO_5$	57.37	5.22	5.58	--
	EtOH	77	(251.24)	57.40	5.24	5.54	--
6d	85-87	Colorless	$C_{13}H_{15}NO_5$	58.86	5.70	5.28	-
	EtOH	66	(265.26)	58.88	5.73	5.31	-
6e	80-83	Colorless	$C_{14}H_{17}NO_5$ (279.29)	60.21	6.14	5.02	-
	EtOH	70		60.24	6.12	5.05	-
7a	186-88	Colorless	$C_3H_5N_3O_3S$ (163.16)	22.08	3.09	25.75	19.65
	EtOH	78		22.07	3.06	25.79	19.68
7b	184-86	Colorless	$C_3H_6N_4O_3S$ (178.17)	20.22	3.39	31.45	18.00
	EtOH	75		20.24	3.37	31.46	18.03
7c	181-83	Colorless	$C_4H_7N_3O_3S$	27.11	3.98	23.72	18.10
	EtOH	77	(177.18)	27.08	3.96	23.74	18.13
7d	179-81	Colorless	$C_4H_8N_4O_3S$ (192.20)	25.00	4.20	29.15	16.68
	EtOH	70		25.03	4.22	29.18	16.65
7e	184-86	Colorless	$C_5H_9N_3O_3S$	31.41	4.74	21.98	16.77
	EtOH	71	(191.21)	31.44	4.75	22.01	16.74
7f	187-89	Colorless	$C_5H_{10}N_4O_3S$	29.12	4.89	27.17	15.55
	EtOH	66	(206.22)	29.15	4.92	27.15	15.57
7g	183-85	Colorless	$C_6H_{11}N_3O_3S$	35.11	5.40	20.47	15.62
	EtOH	68	(205.23)	35.08	5.43	20.50	15.60
7h	173-75	Colorless	$C_6H_{12}N_4O_3S$	32.72	5.49	25.44	14.56
	EtOH	68	(220.25)	32.75	5.51	25.46	14.59
7i	171-73	Colorless	$C_7H_{13}N_3O_3S$	38.34	5.98	19.16	14.62
	EtOH	66	(219.26)	38.31	5.97	19.19	14.65
7j	168-70	Colorless	$C_7H_{14}N_4O_3S$	35.89	6.02	23.91	13.69
	EtOH	69	(234.28)	35.86	6.05	23.93	13.66
9a	171-73	Colorless	$C_{11}H_{13}N_5O_2$	53.43	5.30	28.32	-
	EtOH	63	(247.25)	53.45	5.32	28.35	-
9b	175-77	Colorless	$C_{12}H_{15}N_5O_2$	55.16	5.79	26.80	-
	EtOH	74	(261.28)	55.19	5.82	26.82	-

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Table 2: Spectral Data of Some Newly Synthesized Compounds:

Comp. no	Spectral data
4f	IR ú (cm^{-1}): 3273, 3161 (NH_2); 1655 (C=O); 1621 (C=N) and 1600 (C=C).
4h	IR ú (cm^{-1}): 3277, 3219 (NH_2) 1651 (C=O); 1625 (C=N) and 1601 (C=C). Mass (m/z): 335 (100%); 336 (17.0%) and 337 (5.0 %).
4g	Mass (m/z): 320 (100 %); 321 (3.0 %) and 322 (2.0 %).
5b	Mass (m/z): 275 (100 %); 276 (12.0 %) and 277 (3.0 %).
5f	IR ú (cm^{-1}): 3239, 3123 (NH_2) 1654 (C=O); 1613 (C=N) and 1602 (C=C). ^{1}H NMR δ_H (ppm): 3.08-3.49 (m, 4H, CH-aliph.); 5.80-5.64 (s, 4H, $2NH_2$); 8.16-7.50 (m, 4H, ArH's) and 13.48 (s, 1H, NH) Mass (m/z): 303 (100%); 287 (53%), 243 (13%), 186 (48), 146 (14%) and 120 (15 %).
5h	IR ú (cm^{-1}): 3277, 3219 (NH_2) 1652 (C=O); 1625 (C=N) and 1601 (C=C).
6c	IR ú (cm^{-1}): 3252 (NH); 1735, 1691 (CO's); 1629 (C=N) and 1609 (C=C). Mass (m/z): 251 (100.0%); 252 (15.0%) and 253 (1.2%).
6d	IR ú (cm^{-1}): 3295 (NH); 1721, 1677 (C=O's); 1612 (C=N) and 1601 (C=C). ^{1}H NMR δ_H (ppm): 1.95 (m, 2H, CH_2-aliph.); 2.23 (t, 4H, 2 CH_2-aliph); 3.91 (s, 3H, CH_3) 7.11-7.80 (m, 4H, ArH's) 8.10 (s, 1H, NH) and 10.08 (s, 1H, COOH)**.**
7e	^{1}H NMR δ_H (ppm): 1.90 (d, 2H, NH_2); 2.03 (m, 1H, NHC=S); 2.48-2.53 (t, 4H, $2CH_2$) 8.10 (d, 1H, NHC=O) and 10.07 (s, 1H, COOH)**.**
9a	^{1}H NMR δ_H (ppm): 1.80-2.40 (m, 4H, $2CH_2$); 4.30 (m, 4H, $2NH_2$); 7.52-7.88 (m, 4H, ArH's) and 7.91 (m, 1H, NH)**.**
9b	Mass (m/z): 261 (37%); 188 (100%); 230 (65%); 175 (89 %); 146 (60%); 130 (13%) and 90 (17%).

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